

REMARKS/ARGUMENTS

Reexamination and reconsideration of this Application, withdrawal of the rejection, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the attached evidence and remarks that follow. Claims 1-13 and 15-27 are pending in the application. Applicants note with appreciation that the Examiner has indicated that claims 20 and 21 would be allowable if rewritten in independent form. Claims 15, 16, 26, and 27 are currently withdrawn.

Claims 1-13, 17-19, and 22-24 stand rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,607,687 to Bezwada *et al.* Applicants respectfully traverse this rejection.

In contrast to Bezwada, the present invention discloses chemically crosslinked poly(ethylene glycol) hydrogels (PEG-hydrogels) that degrade in a predictable manner. Weak chemical linkages, e.g., carboxylate ester linkages, are introduced into the hydrogel and provide, in combination with the degree of crosslinking, for the hydrolytic degradation of the hydrogel and the releases of drug molecules that can be trapped within the hydrogel. The hydrogels are broken down to substantially nontoxic PEG-fragments which are usually cleared from the body.

It is further noted that the polyoxaester disclosed in Bezwada *et al.* are substantially linear polymeric molecules. The addition of coupling agents causes branching of long chains, which can impart desirable properties in the molten state to the polyester pre-polymer (column 4, lines 52 to 60). The consequence of introducing a certain degree of branching is the reduction of gelation. In addition, the decrease in viscosity is intended to improve further processing. Branching only means that a polymer chain is not linear but has one or more side-chains, while crosslinking means that two (parallel) polymer chains are connected by connecting molecules. This difference is important because cross-linking, as it is achieved in hydrogels according to the present invention, does not allow further processing. This distinction is important because the Bezwada reference clearly envisions melt processing and solvent casting as possible further processing steps for the disclosed polymers. This type of processing is not possible with a crosslinked polymer structure.

In response to the above arguments, the Examiner has responded that the cited art teaches

an amount of coupling agent that is sufficient to crosslink and that, even if Bezwada only teaches minimal crosslinking, it would be enough to form a gel. Further, the Examiner opines that the reference to “before gelation” in column 4 of Bezwada refers to a method of gelation.

As further support for Applicant’s arguments regarding Bezwada, a declaration from Dr. Molenberg is attached. Dr. Molenberg has worked with crosslinked hydrogel materials for 10 years and currently leads research efforts at Institut Straumann AG, a licensee of this patent application, in the area of PEG hydrogels.

Dr. Molenberg respectfully disagrees with the Examiner’s view of the Bezwada reference. As noted in his declaration, Bezwada is only directed to branching of polymers in the sense of forming side chains on polymers rather than crosslinking as contemplated in the present invention. As explained by Dr. Molenberg and noted in the attached portion of the polymer text, Principles of Polymerization, crosslinking of a polymer material prevents further processing because crosslinked materials cannot be melted and are insoluble. See paragraph 8 of the Molenberg Declaration, page 112 of the attached text where “branching” is clearly defined separately from “crosslinked,” and page 113 of the attached text where crosslinked polymers are described as “insoluble in all solvents” and unable to “flow when heated.”

The Bezwada patent never mentions crosslinking and only refers to “branching.” As noted above, these terms are not synonymous in the polymer art. Further, as noted by Dr. Molenberg, Bezwada expressly relates the amount of coupling agent to be added with the phrase “before gelation occurs,” which also suggests that gelation (i.e., crosslinked gel formation) is not envisioned.

This conclusion becomes inescapable when you read the Bezwada reference as a whole and consider the types of products that are envisioned and the manner in which these products are intended to be processed. As noted in paragraphs 7 and 9 of the Molenberg Declaration, the products described in Bezwada are primarily made by molding, extrusion, or solvent casting. Such techniques require the polymer to be flowable or soluble, neither of which is a characteristic of a crosslinked hydrogel as made clear in the attached polymer text. The fact the Bezwada reference extensively refers to such processing techniques in columns 6-8, combined with the complete silence as to crosslinking, clearly indicates that one would not view Bezwada as teaching a crosslinked hydrogel polymer composition. Instead, as noted in paragraph 7 of the

Molenberg Declaration, the reference in Bezwada to branching (as opposed to crosslinking), which reduces viscosity and tendency to crystallize, is entirely consistent with the description of melt processing and solvent casting, which can be aided by reduced viscosity and reduction in crystallization.

It is further noted that the crosslinked polymeric structures of the present invention undergo extensive swelling in an aqueous environment. In contrast, as noted in paragraph 10 of the Bezwada reference, the polyoxaesters disclosed in Bezwada *et al.* are hydrophobic and therefore do not undergo swelling when they come in contact with water. As a consequence of the swelling in an aqueous environment, for hydrogels according to the present invention, degradation proceeds throughout the whole hydrogel. Polyoxaester materials as taught in Bezwada *et al.* are only degraded on their surface, which greatly reduced their bio-absorbability. Further, it is noted that suture materials are mentioned as a possible application in Bezwada. As mentioned in the attached declaration, swelling of suture material would be undesirable, which provides more evidence that the Bezwada reference does not contemplate use of a hydrogel.

Finally, as noted in paragraph 11 of the declaration, in contrast to the Bezwada disclosure, the hydrolytic degradation of hydrogels of the present invention can be precisely controlled by the degree of crosslinking, by altering the number of methylene groups adjacent to the hydrolytically unstable linkage, and by altering the degree of branching of the PEG polymer (page 6, paragraph [0030] of the specification). Bezwada *et al.* do not describe how the degradability of the polymeric materials described therein may be controlled.

In sum, Bezwada *et al.* teach polymer blends containing two polymers that are not crosslinked. The polymers may comprise PEG components, but the Bezwada patent does not disclose hydrogels. In fact, it is clear that Bezwada *et al.* do not suggest crosslinked polymeric structures forming a hydrogel in any way. Therefore, the subject matter of claim 1, and all claims dependent thereon, is novel over Bezwada *et al.*

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit

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